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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,104	09/27/2000	Alan P. Kozikowski	ZAA-012.01	6012

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EXAMINER

HUANG, EVELYN MEI

ART UNIT PAPER NUMBER

1625

DATE MAILED: 09/09/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/671,104

Applicant(s)

KOZIKOWSKI ET AL.

Examiner

Evelyn Huang

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-59 is/are pending in the application.
- 4a) Of the above claim(s) 19-26 and 45-59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-18 and 27-44 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
- 6) ☐ Other: _____.

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1. Claims 1-59 are pending.

Election/Restrictions

2. In response to the restriction requirement mailed on 2-25-02, applicant has elected group I, claims 1-10, 27-36. In response to Applicant's request for the simultaneous examination of group I, claims 1-10, 27-36 and group II, claims 11-18, the examination has extended to group II, claims 11-18 and group V, claims 37-44.

Claim Rejections - 35 USC § 112(2)

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18, 27-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- a. Claims 1, 27, it is unclear whether these are compound claims or composition claims. A compound of formula (I) alone would not constitute a composition. If composition were intended, the claims should be amended to the composition format, i.e. 'A composition *comprising* a compound of formula (I)'.
- b. Claims 1-18, 27-44, the terms 'comprises' in the definition of the variables of formula (I) is open ended and is therefore indefinite.
- c. Claims 1, 7, 11, 27, 33, 37,
 - What is the 'biomolecule' in the definitions of A, R2-R13, R14? A definition of 'biomolecule' is not found in the specification.
 - What are the groups hanging on the bivalent acyl, ether, sulfonyl, carbonyl, phosphoryl, amido, ester etc? A definition is found in the specification.
- d. Claims 5, 6, 31, 32,

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- It is unclear whether these are compound claims or method of use claims. Amending these claims to the proper format for compound or method claims is recommended.
 - If these were independent claims, the structure of 'formula I' is missing in the claims but is required. If these were dependent claims, the base claim from which they are dependent on is missing but required.
- e. Claims 15, 41,
- The term 'modulation' is indefinite since it embraces the activation and inhibition.
 - The term 'comprises' in 'a disease or condition comprises a disease or condition' is open-ended and is therefore indefinite.
- f. Claims 16, 42, what are the 'other psychiatric or clinical disfunctions'? A definition is not found in the specification.

Claim Rejections - 35 USC § 112(1)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18, 27-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, is enabling only for the exemplified compounds for inhibition of the reuptake of norepinephrine, epinephrine, thereby useful for the treatment of depression, cocaine addiction etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

- a. *Nature of the invention.*

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The instant invention is drawn to a composition comprising a N-3 bridged tropane analog compound and its method of treating disorders or conditions caused by a deficiency in monoamine concentration in a human.

b. *State of the prior art and the level of the skill in the art.*

Monoamine includes norepinephrine (NE), serotonin (5-HT), dopamine (DA), each with its subtypes of receptors and are involved in functions similar or different from one another (Schildkraut, PTO-1449).

Cocaine analogs have been described (Carroll, J. Med. Chem. 1994 (37), 2868, PTO-1449). Bi or tri-cyclic aza compounds derived from tropanes are described by Kozikowski (6150376). Scheel-Kruger also discloses a fused tropane derivative as neurotransmitter reuptake inhibitor (WO 97/16451, PTO-1449).

The level of the skill in the monoamine art is high.

c. *Predictability/unpredictability of the art.*

The high degree of unpredictability is well recognized in the monoamine reuptake art. A slight modification in the structure of the compound would drastically alter its biological activity, as evidenced in the very different potencies of structurally similar substituted phenyl-tropane-carboxylic acid methyl esters (Carroll, page 2866, Table 1) and the very different K_i or IC_{50} values, as well as different selectivity for the various monoamine transporters exhibited by the structurally similar tropane analogs (Kozikowski, column 59, Table 1; Scheel-Kruger, pages 17-18, Table 1). Therefore there is no basis for one of ordinary skill in the art to extrapolate the results of a selected groups of structurally similar compounds to other compounds of diverse structures, especially those having a solid support unit, a polymer or a biomolecule of undefined nature.

d. *Amount of guidance/working examples.*

How to make

Preparation of 8 example compounds limited to A being a double bond, R1 is phenyl, substituted phenyl, naphthyl or furyl, R14 is a carboxylate, is described (Fig. 3). A compound attached to a solid support, a polymer or a biomolecule has not been described.

Starting materials and the process of making the instantly claimed compounds not described in the specification are not seen but required. Sources are particularly pertinent

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especially when the structures of these compounds are not described. Absent sources, the public is offered mere language, rather than enablement. Ex parte Moersch 104 USPQ 122. In re Howarthe 210 USPQ 689.

How to use

The procedure for the assays for assessing the binding affinity and inhibition of reuptake of NE, 5-HT and DA, and the results for the exemplified compounds are found on pages 29-30 of the specification. No in vivo procedures are described.

e. *The breadth of the claims.*

Applicant's assertion that all the structurally diverse compounds embraced by the generic claims (including the highly substituted compounds, especially those with solid support unit, polymer and/or biomolecules) would be effective in treating disorders or conditions caused by a deficiency in any type of monoamine concentration does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability in the art and the limited working examples (paragraphs c, d above).

f. *Quantitation of undue experimentation.*

In view of the high degree of unpredictability in the art, the limited working examples and the fact that the breadth of the claims does not commensurate with that of the objective enablement, the disclosure as presented would not allow one of ordinary skill in the art to make and use all the invention as claimed without undue experimentation (paragraphs b-e above).

Conclusion

5. The closest prior art is Kozikowski (6150376) or Scheel-Kruger (WO 97/16451, PTO-1449).

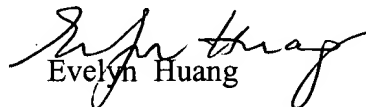
Kozikowski (column 13, lines 18 to 53; column 18, compounds 30, 31, 40; column 57, compounds 6.34. 6.35) or Scheel-Kruger (pages 4-5; pages 24-25, Examples 3, 4, 5) discloses a tricyclic compound derived from tropane, and the composition thereof, are described. However, the prior art compound is a front-bridged or back-bridged compound whereas the instant is N-3-bridged compound.

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6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 703-305-7247. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on 703-308-4698. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



Evelyn Huang

Primary Examiner

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September 5, 2002